1. NAME OF THE MEDICINAL PRODUCT

{Cimetidine tablets 400mg}[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[API and strength:

Each film-coated tablet contains:

Cimetidine, 400 mg]

Excipients with known effect:

No excipient known to have safety concern.

3. PHARMACEUTICAL FORM

White tablets]

<The tablet should not be divided.>

4. Clinical particulars

4.1 Therapeutic indications

Cimetidine tablets are indicated in:

1) Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and there is rarely reason to use cimetidine at full dosage for longer than 6 to 8 weeks (see DOSAGE AND ADMINISTRATION, Duodenal Ulcer). Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of oral cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of oral cimetidine.

2) Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer. Patients have been maintained on continued treatment with cimetidine 400 mg at bedtime for periods of up to five years.

3) Short-term treatment of active benign gastric ulcer. There is no information concerning usefulness of treatment periods of longer than eight weeks.

4) Erosive gastroesophageal reflux disease (GERD). Erosive esophagitis diagnosed by endoscopy. Treatment is indicated for twelve weeks for healing of lesions and control of symptoms. The use of cimetidine beyond twelve weeks has not been established (see DOSAGE AND ADMINISTRATION, GERD).

5) The treatment of pathological hypersecretory conditions (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).

4.2 Posology and method of administration

Duodenal Ulcer

Active Duodenal Ulcer

Clinical studies have indicated that suppression of nocturnal acid is the most important factor in duodenal ulcer healing (see CLINICAL PHARMACOLOGY, Antisecretory Activity, Acid Secretion). This is supported by recent clinical trials (see CLINICAL PHARMACOLOGY, Clinical Trials, Active Duodenal Ulcer). Therefore, there is no apparent rationale, except for familiarity with use, for treating with anything other than a once-daily at bedtime dosage regimen.

In a U.S. oral dose-ranging study of 400 mg at bedtime, 800 mg at bedtime and 1600 mg at bedtime, a continuous dose response relationship for ulcer healing was demonstrated.

However, 800 mg at bedtime is the dose of choice for most patients, as it provides a high healing rate (the difference between 800 mg at bedtime and 1600 mg at bedtime being small), maximal pain relief, a decreased potential for drug interactions (see PRECAUTIONS, Drug Interactions) and maximal patient convenience. Patients unhealed at four weeks, or those with persistent symptoms, have been shown to benefit from two to four weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1 cm and are also heavy smokers (i.e., smoke one pack of cigarettes or more per day) are more difficult to heal. There is some evidence which suggests that more rapid healing can be achieved in this subpopulation with 1600 mg of cimetidine at bedtime. While early pain relief with either 800 mg at bedtime or 1600 mg at bedtime is equivalent in all patients, 1600 mg at bedtime provides an appropriate alternative when it is important to ensure healing within four weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in eight weeks with 800 mg of cimetidine at bedtime.

Other regimens of cimetidine in the United States which have been shown to be effective are: 300 mg four times daily, with meals and at bedtime, the original regimen with which U.S. physicians have the most experience, and 400 mg twice daily, in the morning and at bedtime (see CLINICAL PHARMACOLOGY, Clinical Trials, Active Duodenal Ulcer).

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of cimetidine.

While healing with cimetidine often occurs during the first week or two, treatment should be continued for 4 to 6 weeks unless healing has been demonstrated by endoscopic examination.

Maintenance Therapy for Duodenal Ulcer

In those patients requiring maintenance therapy, the recommended adult oral dose is 400 mg at bedtime.

Active Benign Gastric Ulcer

The recommended adult oral dosage for short-term treatment of active benign gastric ulcer is 800 mg at bedtime, or 300 mg four times a day with meals and at bedtime. Controlled clinical studies were limited to six weeks of treatment (see CLINICAL PHARMACOLOGY, Clinical Trials). A dose of 800 mg at bedtime is the preferred regimen for most patients based upon convenience and reduced potential for drug interactions. Symptomatic response to cimetidine does not preclude the presence of a gastric malignancy. It is important to follow gastric ulcer patients to assure rapid progress to complete healing.

Erosive Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dosage for the treatment of erosive esophagitis that has been diagnosed by endoscopy is 1600 mg daily in divided doses (800 mg twice daily or 400 mg four times daily) for 12 weeks. The use of cimetidine beyond 12 weeks has not been established.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 300 mg four times a day with meals and at bedtime. In some patients it may be necessary to administer higher doses more frequently. Doses should be adjusted to individual patient needs, but should not usually exceed 2400 mg per day and should continue as long as clinically indicated.

Dosage Adjustment for Patients with Impaired Renal Function

Patients with severely impaired renal function have been treated with cimetidine. However, such usage has been very limited. On the basis of this experience the recommended dosage is 300 mg

every 12 hours orally. Should the patient's condition require, the frequency of dosing may be increased to every 8 hours or even further with caution. In severe renal failure, accumulation may occur and the lowest frequency of dosing compatible with an adequate patient response should be used. When liver impairment is also present, further reductions in dosage may be necessary. Hemodialysis reduces the level of circulating cimetidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

4.3 Contraindications

Cimetidine is contraindicated for patients known to have hypersensitivity to the product.

4.4 Special warnings and precautions for use

No special warning.

4.5 Interaction with other medicinal products and other forms of interaction

Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 300 mg four times daily or 800 mg at bedtime of cimetidine concomitantly with a 300 mg twice daily dosage of theophylline (Theo-Dur®*) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg at bedtime regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping the concomitant administration of cimetidine to maintain optimum therapeutic blood levels.

Alteration of pH may affect the absorption of certain drugs (e.g., ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

Additional clinical experience may reveal other drugs affected by the concomitant administration of cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg/kg/day (approximately 8 to 48 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24-month study, there were no differences between the rats receiving 150 mg/kg/day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg/kg/day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Cimetidine has demonstrated a weak antiandrogenic effect. In animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 8 to 48 times the full therapeutic dose of cimetidine, as compared with controls. The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect.

In human studies, cimetidine has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

4.6 Pregnancy and Lactation

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cimetidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse effects reported in patients taking cimetidine are described below by body system. Incidence figures of 1 in 100 and greater are generally derived from controlled clinical studies.

Gastrointestinal

Diarrhea (usually mild) has been reported in approximately 1 in 100 patients.

CNS

Headaches, ranging from mild to severe, have been reported in 3.5% of 924 patients taking 1600 mg/day, 2.1% of 2,225 patients taking 800 mg/day and 2.3% of 1,897 patients taking placebo. Dizziness and somnolence (usually mild) have been reported in approximately 1 in 100 patients on either 1600 mg/day or 800 mg/day.

Reversible confusional states, e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2 to 3 days of initiation of treatment with cimetidine and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine

Gynecomastia has been reported in patients treated for one month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4% of cases while in all others the incidence was 0.3% to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing treatment with cimetidine.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving cimetidine, particularly in high doses, for at least 12 months (range 12 to 79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population.

Heatologic

Decreased white blood cell counts in patients treated with cimetidine (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia.

Hepatobiliary

Dose-related increases in serum transaminase have been reported. In most cases they did not progress with continued therapy and returned to normal at the end of therapy. There have been rare

reports of cholestatic or mixed cholestatic-hepatocellular effects. These were usually reversible. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. However, as in the occasional liver injury with other H2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving cimetidine.

Rare cases of pancreatitis, which cleared on withdrawal of the drug, have been reported.

Hypersensitivity

Rare cases of fever and allergic reactions including anaphylaxis and hypersensitivity vasculitis, which cleared on withdrawal of the drug, have been reported.

Renal

Small, possibly dose-related increases in plasma creatinine, presumably due to competition for renal tubular secretion, are not uncommon and do not signify deteriorating renal function. Rare cases of interstitial nephritis and urinary retention, which cleared on withdrawal of the drug, have been reported.

Cardiovascular

Rare cases of bradycardia, tachycardia and AV heart block have been reported with H2-receptor antagonists.

Musculoskeletal

There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with preexisting arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in the dosage of cimetidine. Rare cases of polymyositis have been reported, but no causal relationship has been established.

Integumental

Mild rash and, very rarely, cases of severe generalized skin reactions including Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma have been reported with H2-receptor antagonists. Reversible alopecia has been reported very rarely.

Immune function

There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

4.9 Overdose

Studies in animals indicate that toxic doses are associated with respiratory failure and

tachycardia that may be controlled by assisted respiration and the administration of a beta-blocker.

Reported acute ingestions orally of up to 20 grams have been associated with transient adverse effects similar to those encountered in normal clinical experience. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 grams of cimetidine, and extremely rare reports following concomitant use of multiple CNS-active medications and ingestion of cimetidine at doses less than 20 grams. An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and 4800 mg of cimetidine intravenously over a 24-hour period experienced mental deterioration with reversal on discontinuation.

There have been two deaths in adults who were reported to have ingested over 40 grams orally on a single occasion of cimetidine.

5. PHARMACOLOGICAL PROPERTIES

Cimetidine is not an anticholinergic agent. Studies have shown that cimetidine inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

Antisecretory Activity

1) Acid Secretion

Nocturnal

An 800 mg oral dose of cimetidine at bedtime reduces mean hourly H+ activity by greater than 85% over an eight-hour period in duodenal ulcer patients, with no effect on daytime acid secretion. A 1600 mg oral dose of cimetidine at bedtime produces 100% inhibition of mean hourly H+ activity over an eight-hour period in duodenal ulcer patients, but also reduces H+ activity by 35% for an additional five hours into the following morning. Cimetidine given as 400 mg twice daily and 300 mg four times daily decreases nocturnal acid secretion in a dose-related manner, i.e., 47% to 83% over a six- to eight-hour period and 54% over a nine-hour period, respectively.

Food Stimulated

During the first hour after a standard experimental meal, a 300 mg oral dose of cimetidine inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent two hours cimetidine inhibited gastric acid secretion by at least 75%.

The effect of a 300 mg breakfast dose of cimetidine continued for at least four hours and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be

maintained by another 300 mg dose of cimetidine given with lunch.

In another study, a 300 mg dose of cimetidine given with the meal increased gastric pH as compared with placebo.

5.1 Pharmacokinetic properties

Cimetidine is rapidly absorbed after oral administration and peak levels occur in 45 to 90 minutes. The half-life of cimetidine is approximately 2 hours. Blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours following a dose of 300 mg.

The principal route of excretion of cimetidine is the urine. Following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound.

Clinical Trials

Duodenal Ulcer

Cimetidine has been shown to be effective in the treatment of active duodenal ulcer and, at reduced dosage, in maintenance therapy following healing of active ulcers.

Active Duodenal Ulcer

Cimetidine accelerates the rate of duodenal ulcer healing. Healing rates reported in U.S. and foreign controlled trials with cimetidine are summarized below, beginning with the regimen providing the lowest nocturnal dose.

5.2 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S. No.	Ingredient	Specification Reference	Qty. per Tablets (mg)	Qty. for total Tablets (Kgs)
1.	Cimetidine	USP	400	40
2.	Starch		30	3
3.	Dextrin		10	1
4	Hydroxypropyl cellulose		10	1
5	Magnesium stearate		10	1
	Sodium starch glycolate		10	1
---	**TOTAL**		**470.0**	**47.0**

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Strength	Packaging size	Primary packaging component
400 mg	20 Tabs/strip/box	aluminum plastic foamed mask package

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. <APPLICANT/MANUFACTURER>

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